REMARKS

Reconsideration of the instant application is respectfully requested in view of the amendments above and the following remarks. The specification has been amended to correct a typographical error related to the priority date of the present invention. The Claims have also been amended to clarify the osteoinductive proteins contemplated. Based on the foregoing amendments, Applicants contend that the present application is in a condition for allowance.

Applicants invention is directed *inter alia* to methods of inducing bone formation in a mammal comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and at least one isolated osteoinductive region of an LMP-1 protein or an LMP-3 protein.

A. Overview

In the final office action of May 15, 2008, the Examiner objected to the specification and reiterated her rejections of the currently pending claims under 35 U.S.C.§ 103(a). With respect to the objection of the specification, the Examiner stated that the filing date of the provisional application 60/132,021 was incorrectly disclosed as 4/30/1997. The Examiner stated that the correct date should read 4/30/1999.

The Examiner also reasserted her rejections of currently pending claims 7-15, 21-30, and 36-40 under 35 U.S.C. 103(a). Specifically, claims 7-15 and 36-40 were rejected as obvious over Hair et al (U.S. 6,521,750) or (U.S. 858,431)[sic] in view of Nagahara et al. Claims 7-15, 21-30, and 36-40 were further rejected as obvious over Boden et al. in view of Nagahara et al. and van Beuningen et al. The reasoning for each of these rejections was unchanged from the previously issued non-final office action of October 25, 2007. To this end, the Examiner maintained that Hair et al., Boden et al., and Beuningen et al. each provided an osteoinductive polypeptide and that Nagahara et al. teaches the use of a transduction domain region. With regard to the priority of the currently pending claims as being earlier than these references, the Examiner stated that the currently pending claims were not entirely supported within the cited parent application. Accordingly, the Examiner stated that the instant application was only entitled a priority date of 3/24/03.

Finally, the Examiner maintained her rejection of claims 7-11 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,858,431, in view of Nagahara et al.

Applicants have addressed each of the foregoing objections and rejections herein. More specifically, Applicants have amended specification to correct the foregoing clerical error cited by the Examiner and, amended the claims so as to overcome the Examiner's rejections. For the reasons discussed herein, Applicants respectfully request entry of these amendments and assert that the present application is in a condition for allowance.

B. Objection to the Specification

As indicated above, Applicants have amended paragraph [0001] of the present specification so as to correct a clerical error in the priority date of U.S. Provisional Application No. 60/132,021. To this end, as amended, the specification now provides the correct filing date of Apr. 30, 1999 for U.S. Provisional Application No. 60/132,021.

C. Rejections based on 35 U.S.C § 103

With respect to rejections based on Hair (U.S. Patent 6,521,750) and Boden (Endocrinology 1998, 139(12): 5125-5134), Applicants respectfully maintain that the specification of the instant application is supported by the specifications of PCT application PCT/US00/11664 filed on April 28, 2000, U.S. application Ser. No. 09/959,578, filed Jun. 21, 2002; and U.S. Provisional Application No. 60/132,021, filed on Apr. 30, 1999. As a result, Boden and Hair cited by the Examiner, are not proper prior art references and Applicants reserve the right to prosecute the original claims, as filed, in a continuation application. Nevertheless, for purposes of expediting prosecution of the present application, Applicants have amended the claims as set forth herein.

As set forth above, Applicants have amended the presently pending claims so as to clarify the osteoinductive polypeptides of the present invention. More specifically, Applicants have amended independent claims 7, 21, and 36 to recite that the fusion polypeptide is comprised of at least one isolated osteoinductive region of either an LMP-1 or an LMP-3 protein. As recited herein, these isolated polypeptides demonstrate osteoinduction (per claim 7), proteoglycan synthesis (per claim 21), or osteoblast differentiation from progenitor cells (per claim 36). Dependent claims 10, 24, and 39 have been further amended to recite that such polypeptides are comprised of any one or combination of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, and SEQ ID NO 8. Dependent claims 11,

25, and 40 were also amended to recite that the osteoinductive polypeptides are comprised of either SEQ ID NO 7 or SEQ ID NO 8.

Support for the foregoing amendments may be found within the specification of the present application. Specifically, at least ¶ 0031 states that the preferred osteoinductive peptides include regions derived from RLMP, hLMP-1, hLMP-1s, hLMP-2, and hLMP-3. To this end, the contemplated polypeptides are not comprised of the entire nucleic acid or protein sequences. Rather, they are isolated from the osteoinductive regions of the original sequence. Further to this, ¶ 0023 *et seq.* further provides an exemplification of such osteoinductive regions of the LMP protein spanning at least amino acids 94-133 of human LMP-1 (hLMP-1) and hLMP-3. Polypeptides in and around these regions, exemplified as SEQ ID NOS 1-8, were further demonstrated in the Examples section of the present application as having osteoinductive functionality and inducing proteoglycan synthesis. Accordingly, no new matter was introduced in the present amended claims.

None of the references cited by the Examiner in her rejection under 35 U.S.C. 103(a) teach or provide for inducing bone formation, proteoglycan synthesis or osteoblast differentiation using a combination of a protein transducer and an isolated osteoinductive region of an LMP-1 protein or an LMP-3 protein. Referring first to Boden et al., this publication specifically relates to the first identification of LMP-1 in rats and its function in calvarial osteoblast differentiation, particularly with respect to bone formation. Boden does not teach or provide for inducing bone formation, proteoglycan synthesis or osteoblast differentiation using a combination of a protein transducer and an isolated osteoinductive region of an LMP-1 protein or an LMP-3 protein.

Hair et al. (referring to US6521750 or 6858431) is similarly deficient in that there is no discussion or experimentation related to isolating and administering polypeptides from an LMP's osteoinductive region. More particularly, Hair et al. presents the next generation to Boden et al. in that these patents relate to the discovery, isolation, and potential uses of a rat LMP (rLMP) gene, a human LMP (hLMP) gene, and a truncated version of human LMP-1 (hLMP-1s). To this end, Hair et al. first provides the nucleic acid sequences and amino acid sequences for each of these LMP genes, then further characterizes gene therapy methods of using these sequences so as to facilitate bone formation. However, much like Boden et al., Hair et al. stops short of identifying the specific osteoinductive regions within these proteins. Rather, each of the foregoing nucleic acid sequences and protein sequences of Hair et al. are only contemplated for

administration in their entirety. As is true with Boden, there is nothing within Hair et al. to teach which region(s) of these genes are actually functional for bone formation or that such regions may be specifically isolated and administered in accordance with the present invention.

The remaining references cited by the Examiner are not relevant to the isolation and administration of osteoinductive regions of an LMP protein. Specifically, Beuningen et al. relates to local application of BMP-2 for the stimulation of proteglycans, i.e. synthesis of cartilage. There is no discussion within Beuningen et al. relating to the LMP protein. Nagahara et al. also does not teach any aspect of the LMP protein. While the Examiner is correct that Nagahara et al. provides an overview of steps to creating a TAT fusion protein, the specific protein discussed is p27. There is no discussion of any osteogeneic protein, let alone LMP.

Based on the foregoing, there is nothing within the prior art to teach or suggest that any one particular region of the previously known LMP protein is responsible for osteoblast differentiation and/or proteoglycan synthesis. Rather, at best, the references cited by the Examiner teach isolation and characterization of an entire LMP protein. Furthermore, there is nothing in the prior art to provide for the isolation of polypeptides within an osteoinductive region of an LMP protein such that, upon administration, the polypeptides will provide for osteoinductive functionality, proteoglycan synthesis, or osteoblast differentiation. As noted above, the foregoing claims have been amended to include such peptides isolated from such osteoinductiv regions. For at least these reasons, Applicants respectfully assert that the present claims, as amended, traverse the Examiner's rejection. Accordingly, Applicants respectfully request that the Examiner withdraw her rejections under 35 U.S.C. 103(a) and allow these amended claims.

D. Double Patenting Rejections.

Applicants also assert that the presently amended claims overcome the Examiner's double patenting rejections. Specifically, in the Final Office Action of May 15, 2008, the Examiner rejected the claims of the instant application under nonstatutory obviousness-type double patenting over claims 1-13 of U.S. Patent No. 6858431 ("the '431 patent"), in view of a combination of Nagahara et al.

Applicants respectfully assert that the foregoing amended claims traverse the Examiners non-statutory obviousness-type double patenting rejection because not all of the claim limitations are taught by the cited references. The Examiner is respectfully reminded that, when the

conflicting claims are not identical, a nonstatutory obviousness-type double patenting rejection is only appropriate where at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Accordingly, the first determination in a nonstatutory obviousness type rejection is similarity of the claims. If non-identical, the second question is whether the prior art reference anticipates or renders obvious the claimed invention (See MPEP 804(II)(B)(1)). If there is no anticipation or obviousness, then the nonstatutory obviousness-type double patenting rejection cannot stand.

As set forth above, Applicants have amended the presently pending claims so as to clarify the osteoinductive proteins of the present invention, thereby presenting a claim set non-identical to that of the '431 patent. The '431 patent claims a method of inducing bone formation in progenitor cells by transfecting the cells with a cDNA sequence encoding the full length human LMP-1 protein (See Examples 22 and 23). As shown above, however, the claims of the present invention were amended to recite that the osteoinductive protein is comprised of at least one isolated osteoinductive *polypeptide* from an osteoinductive region of an LMP-1 or an LMP-3 protein. Accordingly, unlike the claims of the '431 patent, the claims of the present invention relate to *polypeptides*, not a nucleic acid sequence. Moreover, the claims of the present invention are comprised of polypeptides of an osteoinductive region of the LMP protein, not the full length protein as taught by the '431 patent. Accordingly, the present claims are not identical to that of the '431 patent.

As discussed above, the present claims are also not obvious over the '431 patent in view of Nagahara et al because neither of these references teach or provide for a polypeptide isolated from an osteoinductive region wherein the polypeptide demonstrates osteoinductive functionality, proteoglycan synthesis or osteoblast differentiation upon administration. Specifically, the '431 teaches and claims a full length rat LMP (rLMP) gene, a full length human LMP (hLMP) gene, and a truncated versions thereof for potential use in gene therapy. The '431 patent first provides the nucleic acid sequence and amino acid sequence for each these LMP genes, then further characterizes methods of using these sequences as a form of gene therapy for facilitating bone formation. As indicated above, the '431 patent stops short of identifying the

specific osteoinductive regions within these proteins. Rather, each of the foregoing sequences of the '431 patent are contemplated for delivery in their entirety. There is nothing within the '431 patent to teach which region(s) of these genes are actually functional for bone formation or that such regions may be specifically isolated and administered in accordance with the present invention.

Nagahara et al. does not account for this deficiency. Rather, Nagahara et al. only provides an overview of steps to creating a TAT fusion protein. There is no discussion of any osteogeneic protein, let alone LMP.

Based on the foregoing, there is nothing within the prior art to teach or suggest that any one particular region of the previously known LMP protein is responsible for osteoblast differentiation and/or proteoglycan synthesis. Rather, at best, the references cited by the Examiner teach isolation and characterization and administration of an entire LMP protein in the form of a nucleic acid. Furthermore, there is also no teaching of a specific and isolated region of the LMP protein that, upon administration, will demonstrate osteoinductive functionality, proteoglycan synthesis, or osteoblast differentiation. Accordingly, the '431 patent and Nagahara et al. in combination do not render the present claims as obvious. Based on the holding in *In re Berg*, Applicants respectfully assert that the present claims, as amended, traverse the Examiners rejection, and Applicants respectfully request that the Examiner withdraw her nonstatutory obviousness-type double patenting rejection and allow these amended claims.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns, and the claims of the instant application are in condition for allowance. Applicants request that any questions concerning this matter be directed to the undersigned at (609) 844-3020.

Please charge any deficiency and/or credit any overpayment to Deposit Account No. 50-1943. Thank you for your kind consideration in this matter.

Respectfully submitted,

Date: August 11, 2008

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